

THE '3P PROJECT'

An overview of the 3P proposal to accelerate innovation and access for new treatment regimens for TB

WHY THE '3P PROJECT' FOR TUBERCULOSIS IS NEEDED

Tuberculosis (TB) mainly affects low- and middle- income countries with 95% of cases occurring there. 1.3 million people were killed by the disease in 2012 and there were 8.6 million new cases requiring treatment. With the advent of new diagnostics like GeneXpert the confirmed numbers of multidrug-resistant (MDR) TB cases are rising and programmes are unable to cope - 16,000 patients diagnosed with MDR-TB in 2012 did not receive treatment. And about 80% of those estimated to have MDR-TB are not even diagnosed.

MDR-TB treatment is particularly difficult, because it is long—two years of treatment including eight months of daily injections and a total of more than 14,600 pills to swallow—and because many of the medicines used have toxic side effects such as deafness, psychosis and severe nausea. Moreover, the success rate is unacceptably low with only 48% of patients being cured, and costs can be very high. For 9% of global cases with extremely drug-resistant TB (XDR-TB) treatment is even longer, more expensive and the success rate is even lower at only 13%.

The ultimate goal in TB treatment is the development of new treatment combinations to effectively, safely, quickly and simply treat all forms of TB. In the immediate term there is an urgent need to improve the treatment for MDR-TB. In order for these new treatment combinations to be developed the status quo must be transformed to deliver:

- **a healthy TB drug pipeline** with a number of compounds in all phases of development
- **an increase in investment;** the current spending of \$627.4 million on all TB R&D (vaccines, diagnostics and treatment) is only 30% of the \$2 billion annual funding target outlined in the 2011–2015 WHO Global Plan. Moreover, investments are decreasing, with the private sector having reduced its investments by 22.1% in 2012.
- **an open collaborative R&D approach** that reduces risks and costs associated with testing multiple drugs for combination treatments by incentivizing research organizations to share scientific data, clinical trial results as early as possible and to conduct medically appropriate research on combinations of compounds.

SUMMARY OF THE '3P PROJECT'

The aim of the '**3P Project**' is to rapidly deliver affordable, effective new regimens for TB through an open collaborative approach to conducting drug development and through novel approaches to financing and coordinating R&D. The 3P Project implements three mechanisms to facilitate the necessary and appropriate R&D for TB regimens:

- **push** funding to finance R&D activities upfront (i.e. through grants)
- **pull** funding to incentivise R&D activities through the promise of financial rewards on the achievement of certain R&D objectives (i.e. through milestone prizes)
- **pooling** of intellectual property (IP) to ensure open collaborative research and fair licensing for competitive production of the final products

BACKGROUND: WHY IS TB DRUG R&D FAILING TB PATIENTS?

FOCUS ON DEVELOPMENT OF SINGLE DRUGS, NOT NEW REGIMENS. In 2012, the first new TB drug in 50 years received accelerated approval for use in treating MDR-TB, and a second new drug was approved in late 2013. TB must be treated with a combination of drugs, but a lack of collaboration and transparency means that clinical trials to test these two new drugs in combination in order to ensure they can be safely combined and then to build a new, better regimen will not be completed for several years. Many organisations working in the area of regimen development, including TB Alliance, the UK's Medical Research Council (MRC), the Open Source Drug Discovery project (OSDD) and RESIST TB, have

encountered obstacles in accessing new drug compounds for testing as part of improved treatment regimens. There is currently no IP licensing mechanism linked to financial incentives – either grants or prizes - to incentivize the collaborative, open research needed to stimulate regimen-based R&D activities.

INADEQUATE FINANCIAL INCENTIVES FOR COMPANIES. The market for TB regimens is far less lucrative than for other diseases and is marked by chronic underinvestment; this translates into slow or stalled scientific progress, as promising drug candidates languish for lack of a business case. Commercial developers actually reduced investment in TB drug R&D between 2011 and 2012: Pfizer withdrew from the TB R&D field entirely, Otsuka decreased its drug discovery investments, AstraZeneca decreased funding and slowed clinical trials for its TB drug candidate AZD-5847, and in early 2014 announced that it would stop all early-stage research into neglected tropical diseases, TB and malaria. The lack of market incentives makes it difficult for research organizations to enter the TB R&D field and to take TB drug candidates through to late-stage clinical research, leaving significant gaps in the pipeline: there are no TB drugs in Phase I clinical development and no late-stage clinical projects to test all-new drug regimens. Many of the compounds currently in Phase II and Phase III are older “repurposed” compounds that don’t represent investments by commercial developers. With the exception of PA-824, new drugs are currently being developed as single products and are not involved in combination trials or new regimen trials until after receiving regulatory approval.

LACK OF FINANCIAL SUPPORT TO PROGRESS PRECLINICAL COMPOUNDS. In early-stage and preclinical research, the majority of TB compounds are being developed by public institutions, small companies or product development partnerships (PDPs), and it is unclear if they have the necessary capital and resources to bring an adequate number of new products forward to Phase I trials. For example preclinical development of the new drug candidate PBTZ169 was funded by the European Commission, but further progression of this potential new chemical entity has stalled as there are no dedicated funding streams available for the next stage of development.

Opening up the pipeline to promote collaboration for drug combinations and regimen development and offering incentives to facilitate progression will help ensure that preclinical compounds are brought forward to clinical trials. Drug-drug interaction and potential beneficial drug combinations can be discovered sooner if products are tested together at an early stage, which will accelerate the development of new regimens.

ACCESS AND AFFORDABILITY NOT GUARANTEED: When new TB products come to market, they may not be affordable or accessible in countries where the disease burden is highest. For example, the new TB drug bedaquiline will cost \$900 in low-income countries and \$3,000 in middle-income countries for a 6-month regimen, to which the cost of several other drugs will need to be added.

THE 3P PROPOSAL: A JOINT POOLING & FUNDING MECHANISM TO PROMOTE INNOVATION AND ACCESS

The ‘3P Project’ (Push, Pull, Pool) proposal creates a new open collaborative framework for regimen development based on the sharing of data, the pooling of intellectual property and the creation of incentives for multiple actors to enter the R&D process in order to accelerate development timelines. The proposal seeks to leverage as much existing capacity and expertise in TB as possible to foster greater collaboration between researchers and developers. As mentioned above, there are several different organisations working on aspects of TB drug R&D, but without the necessary incentives and co-ordination they have not yet been able to produce the new regimen required. The 3P proposal does not seek to duplicate or replace the work of these organisations, but rather to create an overarching framework to further facilitate this work through the provision of additional incentives and an open collaborative framework to stimulate progress.

In order to ensure affordability of the final medicines, the 3P Project separates (or “de-links”) the cost of R&D from the price of the resulting treatments. De-linkage also paves the way for more rational antibiotic stewardship and negates the need for unnecessary marketing strategies to boost sales.

STEP 1: INCENTIVIZE COLLABORATIVE EARLY-STAGE RESEARCH: Creativity and novel approaches are especially important in the earliest phases of drug discovery, when potential drug candidates are identified. Milestone prizes are particularly well-suited for spurring innovative effort from a large,

diverse pool of Research Organizations (ROs) who could be working anywhere worldwide with a wide range of scientific approaches. (Note that ROs could include academic, public, non-profit, or private labs, from small- to large-scale). To facilitate research on combinations of medicines, the project would use relatively small (see chart) milestone prize funding to reward the licensing of intellectual property rights (IPR) for potential new TB drugs to a patent pool, a central component of the open collaborative framework-during the early ('discovery') phase of research (see chart). ROs would share all relevant scientific data to enable collaborative research and avoid costly duplication of efforts. Drug candidates for the pool would be selected by a Technical/Scientific Advisory Committee using a Target Product Profile (TPP) as a basis for the evaluation.

STEP 2: FORTIFY AND ACCELERATE PRECLINICAL DEVELOPMENT: Compounds that have progressed through the stages of lead optimization, preclinical and GLP toxicity studies (where there is a very high attrition rate of compounds) and are ready to enter clinical development (Phase I) would be candidates for medium (see chart) milestone prizes. Such prizes would be used to spur the development of compounds already in the open collaborative framework and to attract in new compounds from outside. The milestone prizes would be awarded on the condition that all relevant IPR are licensed to the patent pool (if not already) and all research findings openly published. For compounds licensed in earlier in the R&D process, the mechanism would also make available, on a discretionary basis, grants to fund further preclinical research, such as GLP toxicity studies for promising compounds (as assessed by a Technical/Scientific Advisory Committee). Both grants and prizes are offered on the understanding that different ROs may need different incentives depending on their access to alternative sources of funding.

STEP 3: ACCELERATE REGIMEN-BASED CLINICAL DEVELOPMENT: As with Step 2, moving compounds and regimens through Phase I and II trials in Step 3 could be financed through two routes, prizes and grants. The project will offer a large (see chart) milestone prize for a regimen that meets the TPP and successfully completes Phase IIb studies. Alternately, ROs could apply for grant funding to carry out Phase I and II trials on promising regimens (as assessed by the Technical/Scientific Advisory Committee). Neither milestone prizes nor grants would be available for single drugs, but rather, would be restricted to drug regimens, unless the specific studies were deemed necessary to demonstrate clear activity or benefit of the single test drug in the context of regimen development. If the relevant IP for research and production had not yet been licensed to the patent pool, ROs would need to grant such licenses and publish or otherwise share data in order to receive any milestone prizes or grants. To address higher costs, the phase II prizes and grants would be larger than those in the preclinical and discovery phases (see chart).

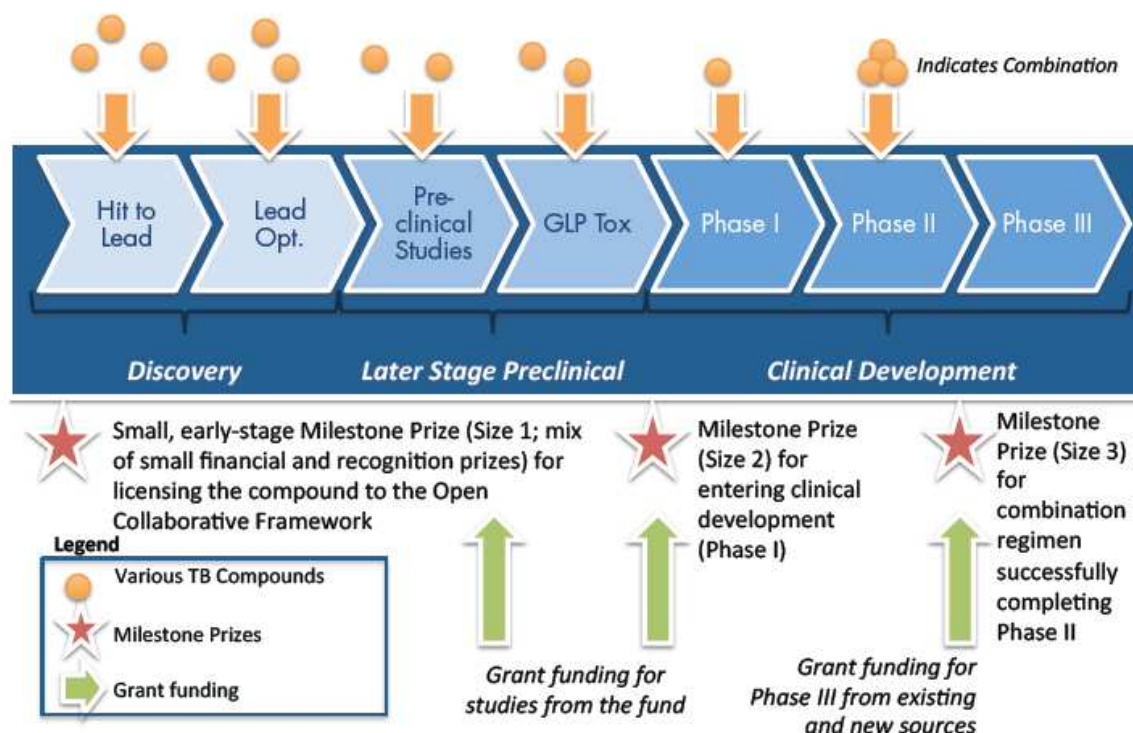
STEP 4: SECURE PUBLIC FINANCING FOR PHASE III TRIALS: By the time compounds have completed Phase II trials, risk and uncertainty are considerably lowered, but costs are exponentially higher. At this point, public funds would be allocated through grants to pay for Phase III clinical trials and submission to stringent drug regulatory agencies and high-burden country drug regulatory agencies. Synergies with existing sources of public funding for clinical trials would be sought.

STEP 5: ENSURE MULTIPLE SUPPLIERS: Once a regimen receives regulatory approval, the individual drugs or fixed-dose combinations could be licensed to one or multiple manufacturers through the pool, allowing competition to lower prices to a sustainable level. Regimen prices would be determined independent of the cost of R&D. Given the high numbers of patients, the volumes of drugs required for DS-TB would potentially be large; therefore, production would benefit from economies of scale. Multiple manufacturers with proven capacity to produce quality-assured drugs (stringent regulatory authority (SRA)/WHO Pre-Qualification) and deliver them in a timely manner (whether originator companies, generic companies, local producers, or other) would be eligible for licenses to manufacture. For DR-TB, if volumes are small, production could be carried out by just one or two of the handful of existing DR-TB drug manufacturers that have received SRA/WHO Pre-Qualification. If DR-TB drug volumes increase with improved access to diagnostics, as is hoped, and if a pan TB regimen is eventually developed, production could eventually transition to a larger number of competing producers.

LICENSING: a central feature of this proposal is to incentivize the pooling of the relevant IP at the earliest stages to ensure that open, collaborative approaches to R&D are facilitated, and to ensure that the IP for the final product(s) is made widely available to ensure equitable access. At each stage where grant or prize funding is made available, a condition of receiving funding will be to license any existing IP on a target compound into the patent pool. Thus, the size of the grant or prize funding will have to be carefully calibrated to ensure that it serves as a real incentive for IP holders to participate in the patent pool. Where such incentives are not sufficient, royalty-bearing licenses could be negotiated between the patent pool and the IP holder(s). These licenses will enable any interested RO to engage in a wide area of research, including the ability to investigate the compound in combination with other compounds. In turn, as a condition for taking a license, the RO will be contractually obliged to publish the results of its research. Moreover, the licenses in the patent pool will stipulate that any further IP (including know-how) that is generated as a result of a RO's participation in the patent pool will be licensed back into the pool on similar terms and conditions. Thus, once a regimen is successfully developed and approved, all the necessary IP will already have been licensed in the patent pool. This IP would then be made available for out-licensing to interested and qualified licensees that can manufacture affordable, quality-assured products.

FINANCING: The total estimated cost of the project ranges from \$83 million to \$250 million. The low figure represents the estimated R&D cost for a regimen composed of four novel drugs taken from the discovery phase through to proof of concept (completion of Phase IIb), or how much it costs to push fund the entire process. However, the attractiveness of a funding mechanism that only reimburses costs is debatable; therefore, the higher figure triples R&D costs to provide a more compelling incentive. The final figure would need to be validated through a pharmacoeconomic analysis taking into account the public health value of the regimen. None of the estimates include the cost of Phase III regimen trials. As the Phase III trials are substantially “de-risked” in this case, Phase III should be grant-funded, likely through existing sources, such as the European & Developing Countries Clinical Trials Partnership (EDCTP). Financing is anticipated to be provided by a consortium of public and private funders, including governments of TB-endemic countries. Given the current shortfall in TB R&D funding, it is critical that such funding be in addition to or via leveraging of current funding.

Schematic representation of the proposed mechanism including prizes, grants and patent pooling:



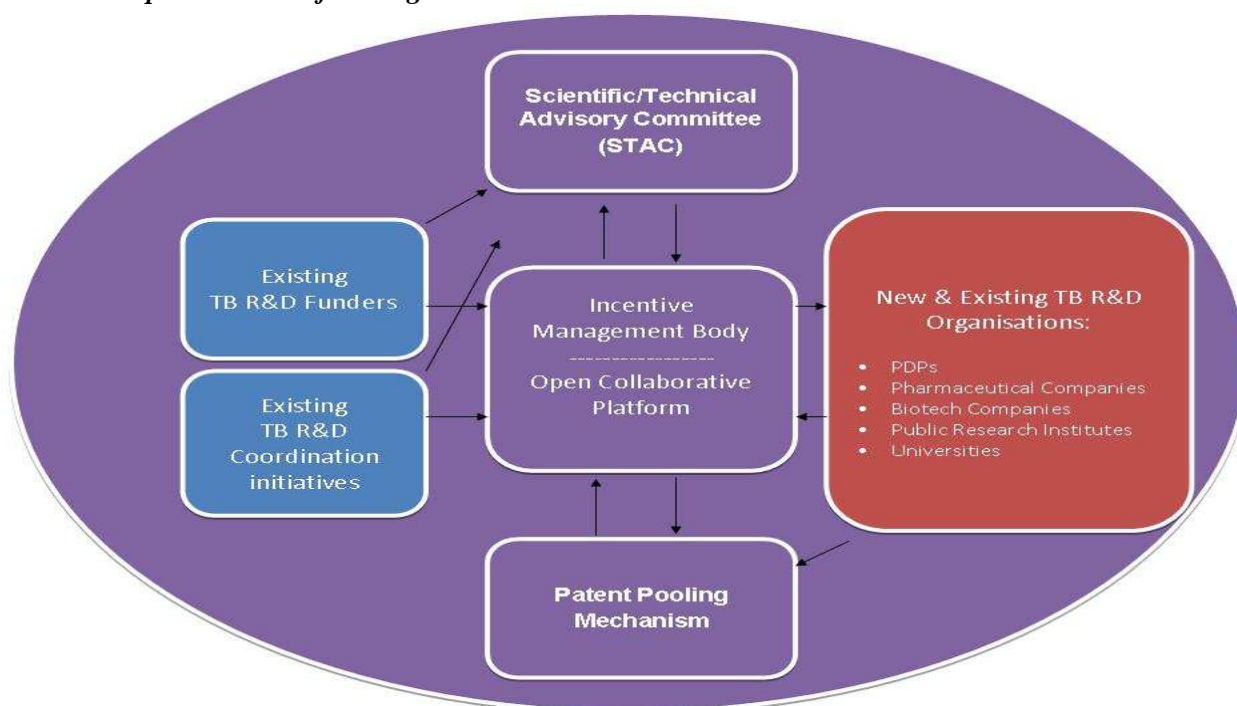
VIRTUAL ORGANISATIONAL STRUCTURE:

The 3P project could be established as a virtual structure with the four key project elements housed separately or in combination within the existing TB R&D architecture.

The four key elements of the virtual structure and their respective roles are:

1. A Scientific/Technical Advisory Committee (STAC)
 - agrees the TPPs and TRPs (Target Product and Regimen Profiles), including confirming the use of existing profiles where appropriate
 - sets TB drug regimen R&D priorities
2. Incentive Management Body covering financing & disbursement
 - manages donor contributions
 - determines the size of the incentives (grants and prizes) to be awarded
 - manages grant and prize disbursement
 - is linked formally to the STAC to ensure incentives follow agreed priorities
3. Open Collaborative Platform
 - provides a portal for potential collaborators to access information on which compounds are available
 - facilitates the open publication and sharing of all research findings within the collaborative framework
 - is the public face of the 3P project; it may be part of or actively collaborate with existing entities in the TB R&D landscape
4. Patent Pooling Mechanism
 - manages all IP licensing to ensure R&D can take place in an enabling environment
 - facilitates manufacturing of affordable, quality-assured new regimens, fixed dose combinations and appropriate formulations through out-licensing.

Schematic representation of the organisational structure:



The STAC would ideally be hosted by the New TB Drugs Working Group within the WHO TB Department, as this is the norm setting agency for health. It should be linked formally to the incentive management body so that the awarding of financial incentives follows the guidance of the STAC. The incentive management body and open collaborative platform could potentially be hosted together by an existing institution or a new body in partnership with other entities involved in funding and shaping TB R&D. The patent pooling mechanism could be hosted by the Medicines Patent Pool, but this would require a change in mandate, since its scope is currently limited to HIV.

GOVERNANCE: A governance board will be established to oversee the incentive management body and open collaborative platform. Members of the board will include key stakeholders such as those contributing financially to the project; countries with a high burden of TB and civil society representatives from affected communities such as patient groups and health care workers. The STAC and patent pooling mechanisms will likely have existing governance structures in place which the project's governance board will establish formal links to.

CONCLUSION

The 3P Project proposal offers benefits over the current TB drug R&D framework by:

- Reducing duplication of research efforts, thereby saving time and money
- Reducing the risks associated with developing potential combinations early in the R&D process
- Accelerating the development of all-new drug regimens
- Reducing the risk of resistance to new compounds by ensuring their use as part of regimens
- Coordinating disparate sources of funding and linking financial rewards to an obligation to share scientific and clinical data and IPR
- Separating ('de-linking') R&D costs from the final price of the new TB combination regimen

Sources: All TB prevalence and incidence data from: World Health Organization. Global TB report 2013, Executive summary. Available from: http://www.who.int/tb/publications/global_report/gtbr13_executive_summary.pdf; Analysis of TB R&D funding trends from: Frick M., Jiménez-Levi E., Harrington M., (October 2013), '2013 Report on Tuberculosis Research Funding Trends, 2005–2012', Treatment Action Group (TAG); Additional data on R&D expenditure from: Moran M, Guzman J, Henderson K, et al. Neglected Disease Research and Development. G-Finder 2012; Data on R&D pipeline from: <http://www.newtbdrugs.org/pipeline.php>; Analysis of what demonstration projects should do from: Moon S, Rottingen JA. "Demonstrating Progress: Towards a More Equitable Global R&D System." Speaking of Medicine PLoS Blogs. 2013; Médecins Sans Frontières/International Union Against Tuberculosis and Lung Disease. DR-TB Drugs Under the Microscope, 3rd edition. Geneva: Médecins Sans Frontières/International Union Against Tuberculosis and Lung Disease; 2013 Oct, <http://www.msfaccess.org/content/dr-tb-drugs-under-microscope3rd-edition>.